

U.S.S.N. 09/848,664

Filed: May 3, 2001

## AMENDMENT AND RESPONSE TO OFFICE ACTION

## Amendment to the Claims

1. (Currently Amended Twice) A drug delivery composition comprising:
- a) a substrate;
  - b) a bi-domain peptide comprising a first domain that binds heparin or heparin-like compounds with high affinity and a second domain that binds to the substrate, wherein the second domain ~~peptide~~ is covalently bound to the substrate so that the ~~heparin-binding~~ first domain is able to bind to heparin or heparin-like compounds;
  - c) heparin or a heparin-like polymer; and
  - d) a protein growth factor or a peptide fragment thereof having a domain that binds heparin with low affinity, wherein the protein growth factor or the peptide fragment thereof binds with low affinity to the heparin or heparin-like polymer of (c), and wherein low affinity is defined as not binding with heparin at a NaCl concentration of between about 25 mM and 140 mM.

Claim 2 (Previously canceled).

3. (Previously Amended) The composition of claim 1 wherein the domain of the growth factor or peptide fragment thereof is further defined as comprising a length of about 8 to 30 amino acid residues comprising at least 2 basic amino acid residues, a ratio of basic to acidic amino acid residues of at least 2, and a ratio of hydrophobic amino acid residues to basic amino acid residues of at least 0.67.

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4. (Previously Amended) The composition of claim 3 wherein the basic amino acid residues are K or R.

5. (Previously Amended) The composition of claim 3 wherein the acidic amino acid residues are further defined as D or E.

6. (Previously Amended) The composition of claim 3 wherein the hydrophobic amino acid residues are further defined as A, V, F, P, M, I, or L or C when C is involved in a disulfide bond.

7. (Previously Amended) The composition of claim 1 wherein the growth factor or peptide fragment thereof is selected from the group consisting of neurturin, persephin, IGF-1A, IGF-1 $\beta$ , EGF, NGF $\beta$ , NT-3, BDNF, NT-4, TGF- $\beta$ 3, and TGF- $\beta$ 4.

Claims 8-19 (Previously Canceled).

20. (Previously Amended) The composition of claim 65 wherein the substrate comprises fibrin.

21. (Previously Amended) The composition of claim 65 wherein the substrate comprises a synthetic polymer hydrogel.

Claims 22 and 23 (Previously Canceled).

24. (Previously Amended) The composition of claim 64 wherein the heparin or heparin-like polymer has a molecular weight between about 3,000 and 10,000,000 Daltons.

25. (Previously Amended) The composition of claim 64 wherein the heparin-like polymer is a polysaccharide having a molecular weight between about 3,000 and 10,000,000

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Daltons, and having at least one negative charge per two saccharide rings and no more than one positive charge per ten saccharide rings.

26. (Currently Amended Twice) The composition of claim 64 wherein the heparin-like polymer is selected from the group consisting of dextran ~~sulfate~~ sulfates, chondroitin ~~sulfate~~ sulfates, heparin ~~sulfate~~ sulfates, ~~fucan~~ fucans, ~~alginate and alginates~~, and a derivative thereof.

27. (Previously Amended) The composition of claim 1 wherein the molar ratio of heparin or heparin-like polymer to growth factor or peptide fragment thereof is at least one.

Claims 28-56 (Previously Canceled).

57. (Previously Amended) The composition of claim 1 in a vascular graft.

58. (Previously Amended) The composition of claim 1 in an article for treatment of dermal wounds.

59. (Previously Amended) The composition of claim 58, wherein the growth factor is TGF- $\beta$ 3.

Claim 60 (Previously Canceled).

61. (Previously Amended) The composition of claim 1 in an implantable sterilized composition.

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62. (Currently Amended Twice) A method for providing controlled release of a growth factor comprising:

preparing a composition comprising

a) a substrate,

b) a bi-domain peptide comprising a first domain that binds heparin or heparin-like compounds with high affinity and a second domain that binds to the substrate, wherein the second domain peptide is covalently bound to the substrate so that the ~~heparin-binding~~ first domain is able to bind to heparin or heparin-like compounds,

c) heparin or a heparin-like polymer, and

d) a growth factor or a peptide fragment thereof having a domain with low affinity ~~for binding heparin and bound heparin or heparin-like polymer, wherein the protein~~ growth factor or the peptide fragment thereof binds with low affinity to the heparin or heparin-like polymer of (c), and wherein low affinity is defined as not binding with heparin at a NaCl concentration of between about 25 mM and 140 mM; and placing the composition on a wound in need thereof.

63. (Previously Amended) The method of claim 62, wherein the growth factor or a peptide fragment thereof is released by dissociation of the growth factor from the heparin or heparin-like polymer.

64. (Previously Added) The composition of Claim 1, wherein the heparin or heparin-like compound is non-covalently attached to the peptide.

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65. (Previously Added) The composition of Claim 1 wherein the substrate is selected from the group comprising fibrin, collagen and synthetic polymer hydrogels.

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